ORAL ERYTHROMYCIN IN THE TREATMENT OF EARLY SYPHILIS*

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Erythromycin, an antibiotic with a relatively narrow activity spectrum similar to penicillin, is produced by *Streptomyces erythreus* originally isolated from a soil sample collected in the Philippines. In 1953 Keller and Morton (1) found treponemes of the Kazan, Nichols, and Reiter strains highly susceptible to the action of erythromycin *in vitro*. The following year Turner and Schaeffer (2) compared the antitreponemal activity of penicillin in experimental rabbit syphilis with chlortetracycline (I.V.), oxytetracycline (I.V. and I.M.), chloramphenicol (I.M.), streptomycin (I.M.), erythromycin (I.M.), and magnamycin (I.M.). These authors found definite antitreponemal activity with each drug tested, but in each case this activity was considerably less than that of penicillin. The following order of effectiveness was suggested: 1) penicillin, 2) magnamycin and erythromycin, 3) oxytetracycline and chlortetracycline, 4) chloramphenicol and streptomycin.

Noting the increasing problem of penicillin allergy, in 1955 Kolmer (3) compared nine different antibiotics with penicillin in the treatment of acute innoculation syphilitic orchitis of rabbits with the hope of discovering the most effective alternate antibiotics for clinical trial in human syphilis. Kolmer's study, also an evaluation of parenteral therapy, employed intramuscular administration of the tested drugs once daily for ten days. His results differed from the earlier report of Turner and Schaeffer with oxytetracycline showing results comparable to penicillin when given at a dose of 5 mg/kg body weight. Similar results could be obtained with tetracycline at 10 mg/kg and chlortetracycline, bacitracin, magnamycin and erythromycin at a dosage level of 20 mg/kg I.M. daily for a period of ten days. Chloramphenicol was found least effective by this author, requiring 80 mg/kg for a minimal curative dose in early experimental rabbit syphilis.

In the present report the available data on three different treatment schedules for the treatment of early syphilis with erythromycin propionate are presented. The paper summarizes the results obtained in treating 130 darkfield positive cases of primary and secondary syphilis to whom one of the following oral erythromycin treatment schedules was given:

(1) Erythromycin propionate* 250 mg. q.i.d. for 10 days
(2) Erythromycin propionate 500 mg. q.i.d. for 10 days
(3) Erythromycin propionate 500 mg. t.i.d. for 10 days

Preliminary results with schedules No. 1 and No. 2 were reported earlier (5). The series has now been enlarged by increasing the number of patients on these schedules and extending their follow-up. Also, a 15 gram–10 day schedule was added. This study is being pursued in an attempt to demonstrate the minimal dosage of erythromycin that will yield a satisfactory cure rate for the growing population of individuals hypersensitive to penicillin.

METHOD

Patients seen in the Houston Social Hygiene Clinic with dark-field positive syphilis were screened by the interviewer immediately after diagnosis before being accepted into the study. An attempt was made at this time to evaluate the patient's ability to follow directions and willingness to cooperate by returning for follow-up examinations. After completion of therapy all patients were reinterviewed and questioned to determine if the drug had been taken as directed. In addition, patients were asked if side effects had occurred. Follow-up program included monthly clinical and serologic examinations with a lumbar puncture at 12 months post treatment. For many reasons the planned follow-up was not achieved in each case.

With presently available diagnostic technics it is futile to attempt to distinguish between relapse and reinfection; therefore, no attempt was made to do so during this investigation. All patients re-

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Supported by Grants from Abbott Laboratories, North Chicago, Illinois, and Eli Lilly and Company, Indianapolis, Indiana.

Received for publication June 9, 1961.

* Ilosone, furnished by Eli Lilly and Company, Indianapolis, Indiana.

quiring retreatment are labeled as treatment failures.

RESULTS

In the 130 patients treated with erythromycin propionate there have been 6 treatment failures. These failures occurred within the first 6 months of follow-up in 5 out of the 6 cases. The sixth case was discovered at 12 months in the 20 gram–10 day schedule group after an 8-month lapse in observations. Several post-treatment lumbar puntures have been performed in each group with no abnormalities discovered to date.

1. Ten grams of erythromycin given over a ten-day period.

Of 35 patients followed from 1–14 months with erythromycin propionate 250 mg. q.i.d. for 10 days, treatment failures were found in three cases. These failures were discovered at 2, 3, and 6 months respectively. Twenty-one of the 35 patients had adequate follow-up examinations for 6 months or longer. Fourteen of the 35 patients were followed for 9 months or longer. A 14% treatment failure rate is noted at 6 months (3 out of 21) and 21% treatment failures at 9 months (3 out of 14) in those followed for this period. The data also were evaluated by a modified life table

TABLE I

Ten-gram schedule of erythromycin propionate in early syphilis

Time Followed	No. of Patients	No. of Failures	Per Cent of Failures
6 months or longer.....	21	3	14
9 months or longer.....	14	3	21

Modified Life Table Method

Time Followed In Months	Adjusted Total No. of Patients	No. of Failures	Cumulative Retreatment %
1	35.0	0	0.0
2	32.0	1	3.1
3	28.9	1	6.7
4	25.7	0	6.7
5	21.4	0	6.7
6	20.3	1	11.6
7	15.8	0	11.6
8	15.8	0	11.6
9	12.4	0	11.6
10	9.0	0	11.6
11	7.9	0	11.6
12	5.6	0	11.6

TABLE II

Twenty-gram schedule of erythromycin propionate in early syphilis

Time Followed	No. of Patients	No. of Failures	Per Cent of Failures
6 months or longer.....	21	2	10
9 months or longer.....	15	2	13

Modified Life Table Method

Time Followed In Months	Adjusted Total No. of Patients	No. of Failures	Cumulative Retreatment %
1	34.0	0	0.0
2	32.0	0	0.0
3	31.0	1	3.2
4	26.9	0	3.2
5	24.8	0	3.2
6	20.6	0	3.2
7	17.5	0	3.2
8	16.5	0	3.2
9	14.4	0	3.2
10	12.4	0	3.2
11	7.2	0	3.2
12	7.2	1	17.1

method designed to make adjustments for the progressive loss of patients from observation.* This showed a cumulative per cent retreatment of 11.6 at 6 and 9 months. Lumbar punctures were performed on 5 patients in this group at the end of one year and the findings revealed normal cells and protein and a nonreactive VDRL in every instance (Table I).

2. Twenty grams of erythromycin given over a ten-day period.

Of 34 patients followed from 1–13 months with erythromycin propionate 500 mg. q.i.d. for 10 days, one treatment failure was seen at 3 months and another at 12 months. It should be mentioned that the latter patient had been lost to follow-up for 8 months after an initial excellent clinical and serologic response to treatment of secondary syphilis. A 10% failure rate is noted in 21 of 34 patients followed 6 months or longer (2 of 21) and a 13% failure rate in the 15 patients followed 9 months or longer (2 of 15). The modified life table method revealed a cumulative per cent retreatment of 3.2 at 6 and 9 months. This was

* Iskrant, A. P., Bowman, R. W., and Donohue, J. F.: Techniques in Evaluation of Rapid Antisyphilitic Therapy (Method 1), Public Health Reports, **63:** 965–977, 1948.

TABLE III

Fifteen-gram schedule of erythromycin propionate in early syphilis

Time Followed	No. of Patients	No. of Failures	Per Cent of Failures
6 months or longer.....	24	1	4
9 months or longer.....	13	1	8

Modified Life Table Method

Time Followed In Months	Adjusted Total No. of Patients	No. of Failures	Cumulative Retreatment %
1	61.0	0	0.0
2	51.0	0	0.0
3	45.0	1	2.2
4	38.9	0	2.2
5	30.7	0	2.2
6	23.5	0	2.2
7	19.5	0	2.2
8	18.4	0	2.2
9	12.3	0	2.2
10	9.2	0	2.2
11	7.2	0	2.2
12	5.1	0	2.2

raised to 17.1% at 12 months, however, when the previously discussed delinquent patient was returned to follow-up. Lumbar punctures performed in 7 patients in this group followed 12 months or longer revealed normal CSF in each instance (Table II).

3. Fifteen grams of erythromycin given over a ten-day period.

Sixty-one patients treated with erythromycin propionate 500 mg. t.i.d. for 10 days have been followed for 1–15 months. To date only one treatment failure has been found and this was at 3 months. Twenty-four of the 61 patients have had adequate follow-up for 6 months or longer on this schedule with a 4% failure rate (1 of 24). Thirteen patients in this group have been followed 9 months or longer with an 8% failure rate (1 of 13). Again employing the modified life table method a cumulative per cent retreatment of 2.2 was recorded at 6 and 9 months. Lumbar punctures performed on 5 patients followed 12 months revealed normal CSF in every instance (Table III).

COMMENT

An attempt to discover the minimal dosage of erythromycin propionate satisfactory for general use as an alternate antibiotic for the treatment of penicillin sensitive patients with early syphilis has been broadened to include a 15 gram–10 day schedule. Despite attempts at patient orientation by the clinician and interviewer concerning the importance of careful follow-up monthly examinations, the percentage of patients adequately followed after treatment was far from ideal.

Nevertheless, a significant number of patients have now been accumulated and the results suggest that erythromycin propionate in a dosage of 500 mg. t.i.d. for 10 days is adequate therapy for primary and secondary syphilis. It is planned to continue following these patients for a total of 2 years post treatment.

Earlier studies from the Houston Social Hygiene Clinic relating to the treatment of dark-field-positive primary and secondary syphilis with oral erythromycin (4, 5) have resulted in the following schedules being discarded as probably inadequate:

Erythromycin stearate 750 mg. q.i.d. for 3 days
Erythromycin stearate 500 mg. q.i.d. for 5 days
Erythromycin stearate 250 mg. q.i.d. for 10 days

To these probably inadequate schedules erythromycin propionate 250 mg. q.i.d. for 10 days is added at this time.

It is hoped that attempts will be made by other investigators to establish an optimal minimal dosage of erythromycin. Also erythromycin and other alternate antibiotics should be carefully evaluated in the treatment of all stages of syphilis.

In addition to the proven good antibacterial activity of erythromycin in a narrower spectrum than chloramphenicol or the tetracyclines, reported side effects with this drug have been definitely fewer and less severe than with most of the broader spectrum antibiotics. In none of our reported erythromycin series, covering 213 patients, have side effects to the therapeutic agent been a problem or resulted in the discontinuation of treatment. Ninety-three per cent of the cases reported in this study allegedly took their medication for a full 10 days. The remaining patients were in two smaller groups, receiving the drug for only 3–5 days.

SUMMARY

In an earlier report from this Clinic it was noted that 20 grams of either erythromycin propionate or erythromycin stearate* adminis-

* Erythrocin, furnished by Abbott Laboratories, North Chicago, Illinois.

tered orally over a 10-day period was probably satisfactory in the treatment of primary and secondary syphilis.

In this report further evidence is given to support the effectiveness of the 20-gram erythromycin propionate schedule. An additional series of patients treated with a 15-gram schedule (erythromycin propionate 500 mg. t.i.d. for 10 days) is presented and discussed. The latter schedule has yielded only one treatment failure in the 13 patients followed a minimum of 9 months.

On the basis of these preliminary observations, it is felt that erythromycin propionate in the 15-gram schedule gives results equal to the 20-gram schedules. Either the 15 or 20 gram treatment plan should prove satisfactory for early syphilis.

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